

Original article ■

Acute-Phase Inflammatory Response in Patients with Pulmonary Tuberculosis

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SUMMARY

The main issue in patients with pulmonary tuberculosis (PTB) represents the impossibility of the host immune response to express bactericidal function and the sterilization of lesions depends exclusively on the specific antimicrobial chemotherapy.

In order to investigate the value of acute-phase inflammatory response markers in patients with newly confirmed extensive PTB, there was designed a clinical study with 80 patients, of whom 40 had active disease (experimental group), while other 40 had inactive sequellar disease without comorbidity (control group).

The examined groups were homogenous with respect to the patient's general demographic characteristics. In the experimental group, 20.0% of the patients had an initial bacterial infection of the lower respiratory tract, while their average value of acute-phase systemic inflammatory markers was initially, before the antituberculosis treatment, significantly elevated compared to the control group. At the end of the treatment, values of erythrocyte sedimentation rate in the first hour (SE) and serum C-reactive protein (CRP) significantly decreased (SE- $p < 0.001$, CRP- $p < 0.001$), together with the value of the leukocyte count (Le) and serum fibrinogen (Le- $p < 0.001$, fibrinogen- $p < 0.001$). Multivariate linear regression analysis proved a significant correlation between baseline serum fibrinogen level with positive history of contact with active TB patient and initial radiological extent of PTB lung lesions.

The values of the acute-phase inflammatory response markers in active PTB have its clinical significance in the assessment of unfavourable course of disease in extensive disseminated form of PTB as well as in the occurrence of complications associated with low respiratory tract bacterial superinfection.

Key words: tuberculosis, inflammation, fibrinogen

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INTRODUCTION

The term acute-phase of the organism defence is general - it is the system's response to various damaging substances to which it is exposed in order to eliminate them and/or create the necessary conditions for repairing and healing of damaged tissues and organs. On this occasion, different metabolic, hematologic, endocrine, cardiovascular and immune mechanisms are triggered. Blood leukocytosis is registered, followed by a change in the concentration of carbohydrates, triglycerides, lipoproteins and certain oligoelements, as well as the substances marked as acute-phase inflammation reactants, namely also as a non-specific markers of systemic inflammatory activity or serum pro-inflammatory indices (1). A full range of acute-phase response in inflammation implies an increase in acute-phase inflammation proteins, as it is registered in routine laboratory analysis through the acceleration of erythrocyte sedimentation rate, leukocytosis, hypergammaglobulinemia, lower serum level of iron and zinc, with a negative balance of nitrogen products and fever as a clinical symptom (2, 3).

The main problem in patients with pulmonary tuberculosis (PTB) is the inability of the host immune response to exert bactericidal function, while the sterilization of lesions depends entirely on the specific antimicrobial chemotherapy, which is carried out over a period of six to eight months (4, 5). Extensive tissue damage in the PTB may occur by direct action of tuberculosis bacilli and/or, as a result of the influx of inflammatory cells (6). The three main groups of phagocytic cells are: polymorphonuclear leukocytes, tissue macrophages and circulating monocytes. Infiltration of inflammatory chemotactic stimulation occurs in aid of mediators, generated at the site of inflammation, which also activate the metabolic processes of the phagocytic cells (2, 5). During active PTB, *M. tuberculosis* activates macrophages and induces the production of proinflammatory cytokines. Inflammation in the extensive PTB engage numerous cell types and molecules, some of which initiate, amplify, and support the inflammation process, some of them slow it down as part of the recovery of the inflammatory region. In general, acute-phase proteins act as mediators of inflammation, inhibitors of inflammation, "cleaner" products of inflammation, modulation of the immune response regulators repairing damaged tissue (4, 7).

Many authors believe that non-specific serum markers of systemic inflammatory activity have a certain diagnostic value in patients with PTB, but their specificity significantly increased only in the assessment of unfavourable course of disease in acute advancing form of extensive PTB, disseminated or extensive forms, and the occurrence of complications, in terms of bacterial superinfection (5, 8). In the expected favourable course of treatment of pulmonary TB, by using the antituberculous drugs, their serum levels declines to subclinical values

at the end of the initial phase of treatment, fully normalizing at the end of treatment (4, 7).

AIMS

The aim of this study was to establish, examine and evaluate the dependence of the level of acute-phase inflammatory response markers in patients with newly confirmed extensive PTB, in relation to sex and age of the patients, their habit of cigarette smoking, as well as in relation to the characteristic clinical symptoms and signs of PTB, the degree of radiological extent of lung lesions, sputum conversion rate and the effects of the applied antituberculosis treatment.

PATIENTS AND METHODS

The research was carried out as a case-control study involving 80 patients with newly confirmed extensive PTB and tuberculosis sequelae without associated co-morbidities, in the period from January 2005 to December 2012. Following the predefined inclusion and exclusion criteria for entering the study, patients were divided into two groups: experimental group (EG) consisted of 40 patients with newly confirmed extensive PTB, whereas the control group (CG) included 40 patients with tuberculosis sequelae, without co-morbidities. Patients of the EG were treated by a specific antimicrobial chemotherapy regimen for the new cases of TB patients, according to the DOTS strategy, while patients of CG were treated only as needed, by symptomatic therapy (9).

In order to determine the cumulative exposure in all the patients to tobacco smoke, their smoking habits were expressed as index of pack/years (p/y), while the degree of nicotine dependence in smoking patients were evaluated through the Fagerstöm's test (questionnaire) for nicotine dependence (10). The degree of radiological extent of pulmonary TB lesions was determined by scoring system of Snider and associates, where each lung is divided into thirds and each of them, depending on the level of lung lesions, graduate to a four-point rating scale from 0 to 3 points with a maximum score of 18 (11). All patients had microbiological sputum examination according to the National guidelines for diagnosing PTB, as well as detecting the erythrocyte sedimentation rate (SE), leukocyte count in peripheral blood (Le) and serum level of C-reactive protein (CRP) and fibrinogen (9, 12). Follow up was done during the antituberculosis treatment for the patients of the EG (at the beginning and after six months), while in CG only once, initially, during the first clinical examination.

Statistical analysis was carried using a computer. All calculations were performed using SPSS software version 18.0. Comparison of mean values of numerical features between the two groups was performed by Student's t test (Student's t test) or Men-Whitney test (Mann-Whitney U test) when the distribution of values did not

meet the requirements of a normal schedule. The values of characteristics that were measured twice in the same group of patients were compared by Student's *t* test for paired samples or Wilcoxon's Signed Rank test when the distribution of values did not meet the requirements of a normal schedule. Comparison of the incidence of certain categories of attribute characteristics was performed using the Chi square test or Fisher's test (Fisher's exact test) in cases when an expected frequency was less than five. Analysis of the relationship between CRP, SE, Le and fibrinogen level at baseline and factors of interest values was performed by linear regression analysis. They were calculated by regression coefficient (β) and the limits of their 95% confidence intervals. The statistical significance of regression coefficients was checked by *t*-test. If a univariate regression analysis confirms that the dependent variable significantly exerts greater influence than any of the test factors, all of these factors are involved in a multivariate model, using the backward (reverse) methods. The threshold of significance of less than 5% ($p < 0.05$) was used to assess the level of error.

RESULTS

The mean age of patients in EG was 55.8 ± 16.3 years vs. 51.6 ± 17.3 years in control one, with no significant differences ($p = 0.058$), which also related to gender status and body weight ($p = 0.084$). As for the social structure of respondents, retired persons dominated (37.5%) in the EG, while the CG was mainly composed of workers (35.0%). In both groups of patients, the refugees had the lowest proportion in the social structure (5.0%). In relation to the social structure of patients, significant differences were registered in both groups ($p = 0.043$). The ratio of urban and rural populations both within and between the groups of patients showed no significant difference ($p = 0.369$). A previous positive history of contact with a person with active TB was registered in 22.5% of patients in the EG and in 20.0% of CG patients, with no significant differences between ($p = 0.785$).

Cigarette smokers were present in both groups in a significantly larger number, compared to non-smokers and ex-smokers ($p < 0.05$), with no significant differences in the prevalence of the same (EG vs. CG: $p = 0.377$) as well as cumulative exposure to tobacco smoke in active smokers (packs: $1,36 \pm 0,67$ vs. $1,24 \pm 0,43$; $p = 0.468$; years: $29,61 \pm 12,83$ vs. $25,64 \pm 9,25$; $p = 0,228$). A higher average level of nicotine dependence was registered in all smoking patients; however, the values of Fagerstöm's score in both groups were not significantly different (EG- 6.26 ± 2.14 vs. CG- $6,73 \pm 1.9$; $p = 0.431$).

The most common respiratory symptoms in patients of EG were: cough (97.5%), dyspnea (70.0%), and hemoptysis (27.5%), whereas the most common general symptoms were fever (47.5%) and night sweats

(65.0%). The average duration of those symptoms to the first visit to a doctor was 67.55 ± 54.78 days, while 57.5% of patients had the average weight loss of 14.42 ± 9.81 kg. The initial values of the body mass of the examined patients were not significantly different between the groups (EG- 62.98 ± 14.35 vs. CG- 65.40 ± 11.28 , $p = 0.403$). The average sputum conversion rate in EG on microscopy was 2.90 ± 2.07 weeks, and on the culture 4.13 ± 2.24 weeks, while the initial nonspecific bacterial superinfection of the lower respiratory tract (LRTI) was registered in 20.0% of patients. The radiological extent of the lung lesions showed significant differences between EG and CG, as well as the initial values of SE, Le, CRP and fibrinogen ($p < 0.001$).

In the EG, the average Snider's radiological score at baseline was 10.23 ± 4.04 score points and at the end of treatment 3.93 ± 2.44 , which is a significantly lower value ($p < 0.001$) (Figure 1).

In the EG, the average initial values of SE, Le count, CRP and fibrinogen were pathologically elevated and by the end of PTB treatment were significantly decreased to the normal or subclinical values (Table 1).

Univariate linear regression analysis as a significant factor that is associated with the SE values in the first hour in patients of EG, at the beginning of the PTB treatment, confirmed only the initial values of Snider's radiological score. Any increase in the value of the score at the beginning of PTB treatment, in one unit, is associated with an increase in the value of SE by 3.03 mm/1h (95% IP: 0,76 mm/1h to 5,30 mm/1h).

Univariate linear regression analysis as significant factors associated with the Le count in patients of EG, at the beginning of PTB treatment, confirmed active smoking status and Snider's radiological score at the baseline level. In active smokers, an average increase in the Le count by $3.11 \times 10^9/l$ (95% CI: $0.10 \times 10^9/l$ and $6.13 \times 10^9/l$) was registered, compared to non-smokers and ex-smokers, while any increase in the value of Snider's radiological score by one unit was associated with an increase in Le count of $0.36 \times 10^9/l$ (95% CI: $0.01 \times 10^9/l$ to $0.71 \times 10^9/l$) (Table 2). Multivariate linear regression analysis as an important factor associated with the Le count at the beginning of PTB treatment confirmed only active smoking status, with the value of the regression coefficient was identical to that of the univariate analysis.

Univariate linear regression analysis as a significant factor that is associated with the values of CRP at the beginning of the PTB treatment, confirmed only an initial LRTI. In patients in whom the same was recorded, the value of CRP at the beginning of the PTB treatment was on average higher by 40.73 mg/l (95% CI: 1.23 mg/l to 80.22 mg/l) than in the other patients.

Univariate linear regression analysis confirmed that positive history of previous contact with active TB patient and Snider's radiological score at the beginning of treatment are significant factors associated with the values of serum fibrinogen at baseline. In patients with a positive history of contact with active TB patient, the se-

rum level of fibrinogen was on average higher by 2.88 g/l (95% CI: 0.31 g/l to 5.44 g/l), than in patients with a negative history, while any increase in the initial values of Snider's radiological score by one unit was associated with an increase in the serum fibrinogen level of 0.28 g/l (95% CI: 0.01 g/l to 0.55 g/l) (Table 3).

Multivariate linear regression analysis as significant factors associated with the values of serum fibrinogen at baseline level also confirmed a positive history of previous contact with active TB patient and Snider's radiological score at the beginning of PTB treatment. In patients with a positive history of previous contact with

active TB patient, the initial serum fibrinogen level was on average higher by 2.96 g/l (95% CI: 0.53 g/l to 5.39 g/l), than in patients with a negative one, while any increase in the initial values of Snider's radiological score by one unit was associated with an increase in the serum fibrinogen level of 0.29 g/l (95% CI: 0.04 g/l to 0.54 g/l). Regression model as an independent variable contains these two factors and constant regression explains 23% of serum fibrinogen variability at baseline in patients in the sample (coefficient of determination - $R^2 = 0.23$) (Table 4).

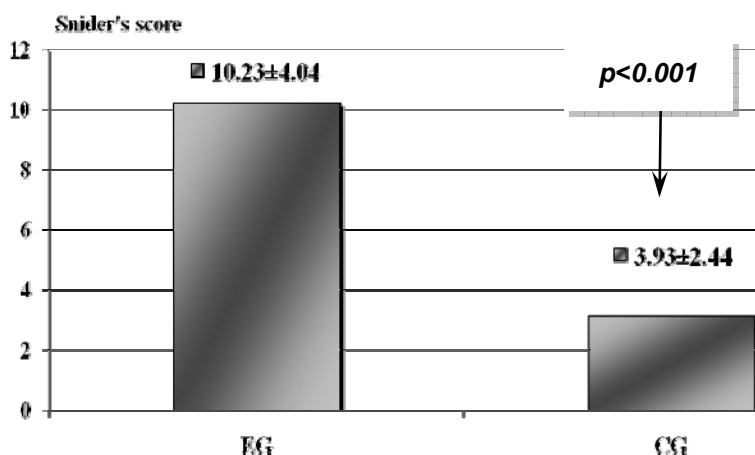


Figure 1. The radiological extent of pulmonary TB lesions at the beginning and at the end of the antituberculosis treatment

Table 1. Comparison of values of non-specific serum markers of inflammation in patients of EG, between the two measurements made and the difference between them

Serum markers of inflammation	Beginning of treatment	End of treatment	Comparison of values (significance)	Difference between values
SE (mm/1h)	67.20±30.54	17.85±17.02	p<0.001	49.35±30.45
Le (x10 ⁹ /l)	9.14±4.59	6.81±2.14	p<0.001	2.33±4.12
CRP (mg/l)	60.97±51.44	7.58±9.23	p<0.001	50.86±46.09
Fibrinogen (g/l)	7.77±3.52	4.57±1.66	p<0.001	3.20±3.43

Table 2. Assessment of correlation factors for inflammation in PTB and the number of Le values at baseline in patients from EG (univariate linear regression analysis)

Factors for inflammation in PTB	β	95% CI for β		P value
		lower	upper	
Smoking habits				
Active smoker	3.11	0.10	6.13	0.043
Ex-smoker	-4.04	-13.49	5.41	0.392
Cumulative exposure to tobacco smoke	pack	-0.86	-3.74	0.545
	years	-0.10	-0.25	0.183
Fargerstöm's score of nicotine dependence	-0.57	-1.47	0.33	0.201
Degree of radiological extent of PTB lesions				
Snider's radiological score (beginning of the treatment)	0.36	0.01	0.71	0.050

Table 3. Assessment of correlation factors for inflammation in PTB and the serum fibrinogen values at baseline in patients from EG (univariate linear regression analysis)

Factors for inflammation in PTB	β	95% CI for β		P value
		lower	upper	
Contact with active PTB patient				
Positive history of previous contact with active TB	2.88	0.31	5.44	0.029
Degree of radiological extent of PTB lesions				
Snider's radiological score (beginning of the treatment)	0.28	0.01	0.55	0.042

Table 4. Assessment of correlation factors for inflammation in PTB and the serum fibrinogen values at baseline in patients from EG (multivariate linear regression analysis)

Factors for inflammation in PTB	β	95% CI for β		P value
		lower	upper	
Constant of regression	4.14	1.28	7.00	0.006
Positive history of previous contact with active TB	2.96	0.53	5.39	0.018
Snider's radiological score (beginning of the treatment)	0.29	0.04	0.54	0.027

DISCUSSION

Because of its location, anatomy and function, lungs are one of the most sensitive organs to oxidative damage. The respiratory epithelium is directly exposed to the various oxidants from open air and tobacco smoke, but also free radicals released by the inflammatory cells in the course of their normal defensive role in the lung. Excessive inflammation in lungs in response to tuberculin protein product and a variety of cell disintegration is the main feature of extensive PTB, commonly associated with non-specific LRTI, which leads to further and significant alterations in clinical course of disease (1, 8). The increased levels of proinflammatory cytokines in plasma, together with the extracellular matrix destruction, suggest that the mechanisms of systemic inflammation in the pathogenesis of the active PTB acts as mutually connected. These processes are the key for further understanding the many effects of systemic inflammatory events in active extensive PTB (2, 6).

Cigarette smoke is one of the external agents which is presumed to be indirectly causally connected as a predisposing factor in the development of PTB. Analysing the smoking habits of the patients in our study, cigarette smokers were present in both groups in a significantly larger number, compared to non-smokers and ex-smokers, with no significant differences in the prevalence of the same between. A high average level of nicotine dependence in all smoking patients was registered, however, the values of Fagerst orm's score in both groups were not significantly different (10, 14).

Although extensive pulmonary TB forms include all cavitary forms, regardless of the size and number of cavitation, the initial extent of pathomorphological changes in the lungs is important, both in the active disease, as well as after curing. Big tuberculous cavities spontaneously, or under the treatment with antituberculosis drugs, often can-not be cured, but depending on the lo-

cation and size and the degree of reparative processes, further lead to the reparative-sequeular lesions in bronchial tree and lung parenchyma, making the morphological and functional damage to the respiratory system (4, 6, 11). In our study, the average Snider's radiological score of patient in EG at baseline was 10.23 ± 4.04 points and 3.93 ± 2.44 at the end of PTB treatment, which is a significantly lower value. The radiological extent of the lung lesions, as well as initial values of SE, Le, CRP and fibrinogen, significantly differed among EG and CG patients. The average sputum conversion rate of patients in EG corresponds to the results in literature (7).

Most of the serum acute-phase inflammatory proteins are created in the liver. Under certain physiological conditions, their serum concentrations are strictly defined limits and depend on the speed of its synthesis in hepatocytes. During the inflammatory processes, particularly in the infection, even in the PTB, their concentration in the serum rises (positive serum pro-inflammatory indices), or decreases (negative serum pro-inflammatory indices) by at least 25%, reaching its maximum between the second and fifth day (4, 5). In our study, in the EG patients, the pathologically elevated mean values of the observed acute phase serum markers of systemic inflammation were registered initially, before starting antituberculosis treatment: SE- $67, 20 \pm 30.54$ mm/h, Le count - $9.14 \pm 4.59 \times 10^9/l$, CRP - 58.45 ± 45.95 mg/l and fibrinogen - $7,77 \pm 3.52$ g/l, which were significantly higher values than those obtained in the CG ($p < 0.001$) and correspond to the available data in literature (4, 7). Infection of great intensity, as it is in active extensive PTB, is often associated with bacterial LRTI superinfection, which is registered in 20.0% of patients in EG, which may explain such high values of CRP (8).

Erythrocyte sedimentation rate (SE) value depends on the sex and age of the patient, physiological sta-

te, body temperature, used drugs, smoking habits, physical activity, morphological characteristics of red blood cells (2). In our study, the average values of SE in the first hour of patients in EG were pathologically increased at the onset of PTB treatment, with significant decrease by the end of the continuation phase of treatment. Univariate linear regression analysis as a significant factor that is associated with the SE values in the first hour at the beginning of the treatment PTB confirmed only the initial values of Snider's radiological score. Therefore, this parameter can be considered as a positive serum marker of initial severity of extensive PTB.

Le count in the peripheral blood along with CRP serum level is the most commonly investigated non-specific serum marker of systemic inflammatory activity in respiratory infections. Patients with active PTB are characterized by mild leukocytosis or leukopenia, neutropenia and rarely lymphocytosis. Many authors have found the correlation between the extent of radiological pulmonary lesions and this hematological parameters in as many as 33% of patients with active PTB with cavitation on initial chest X-ray (1, 4, 15). In our study, in patients of EG, a univariate linear regression analysis confirmed an active smoking status and Snider's radiological score at baseline level as a significant factor associated with the Le count at the beginning of PTB treatment. According to the results in our investigation, Le count in the peripheral blood cannot be recommended as a reliable marker of initial severity of PTB.

Serum level of CRP significantly correlated with the size of infiltrative lung lesions on the chest X-ray in respiratory bacterial infections, including the PTB, while the variations of proinflammatory indices serum levels can be attributed to the initial extent of the lesions in affected lung tissue. Surveys conducted in patients with PTB in the Russian Federation have found up to 5 times higher serum CRP values, which closely correlates with the severity of the clinical course, the radiological extent of the lung lesions and the presence of associated LRTI. The same study indicated that after the three months of antituberculosis treatment, the average serum CRP levels decline to subclinical ones (12 ± 1.9 mg/l). Therefore, this serum inflammatory marker is recommended by authors as a good indicator of response to PTB treatment (13). In contrast, in a study conducted in the UK, it was found that in 15% of patients with active PTB without cavitation on the chest X-ray, the initial value of serum CRP level in most cases was in the normal range (1). In our study, a univariate linear regression analysis as a significant factor that is associated with the values of CRP at the beginning of the PTB treatment, confirmed only an initial LRTI, so it cannot be recommended as a reliable positive marker of initial severity and extensiveness of PTB.

Serum fibrinogen is a positive acute phase protein of systemic inflammation and its value increased during infection, and many other diseases and conditions (older age, smoking habits, diabetes, coronary heart

disease, atherosclerosis). In patients with extensive PTB, serum fibrinogen level showed the highest sensitivity compared to other markers of systemic inflammation during the entire treatment of PTB, especially in the continuation phase of treatment (2, 7). In our study, patients of EG in the expected course of anti-tuberculosis treatment, initially had elevated serum levels of fibrinogen, which was by the end of PTB treatment significantly reduced and completely normalized. Univariate linear regression analysis confirmed that positive history of previous contact with active TB patient and Snider's radiological score at the beginning of treatment are significant factors associated with the values of serum fibrinogen at baseline.

Multivariate linear regression model, as significant factors associated with the values of serum fibrinogen at baseline level, also confirmed a positive history of contact with active TB patient and Snider's radiological score at the beginning of PTB treatment. In patients with a positive history of contact with active TB patient, the initial serum fibrinogen level was on average higher by 2.96 g/l than in patients with a negative one, while any increase in the initial values of Snider's radiological score by one unit was associated with an increase in the serum fibrinogen level of 0.29 g/l. Regression model as an independent variable contains these two factors and constant regression explains 23% of serum fibrinogen variability at baseline in patients in the sample (coefficient of determination - $R^2=0.23$), therefore, it can be recommended as a reliable positive serum marker of initial severity and extensiveness of PTB.

CONCLUSION

The data obtained in this study indicate that certain acute-phase inflammatory response markers have diagnostic value in patients with newly confirmed extensive PTB, especially in assessment of the intensity of the systemic inflammation. However, their specificity significantly increases in assessing the risk of unfavourable course of disease in extensively disseminated forms of disease in terms of further complications, prior to contact with active TB patient, excessive cigarette smoking and concomitant non-specific low respiratory tract bacterial superinfection.

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AKUTNO-FAZNI SISTEMSKI INFLAMATORNI ODGOVOR KOD BOLESNIKA SA PLUĆNOM TUBERKULOZOM

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Sažetak

Osnovni problem kod obolelih od plućne tuberkuloze (PTB) predstavlja nemogućnost imunog odgovora domaćina da ispolji baktericidnu funkciju, te je sterilizacija lezija zavisna isključivo od sprovođenja specifične antimikrobne hemoterapije.

U cilju ispitivanja vrednosti rutinskih markera akutno-faznog sistemskog inflamatornog odgovora kod obolelih od novootkrivene ekstenzivne PTB dizajnirana je klinička studija na planiranih 80 bolesnika, od kojih je 40 bilo sa novootkrivenom dijagnostikovanom PTB (eksperimentalna grupa), a 40 sa posttuberkuloznim sekvelama bez komorbiditeta (kontrolna grupa).

Ispitivane grupe su bile homogene u odnosu na opšte demografske karakteristike bolesnika. U eksperimentalnoj grupi obolelih 20.0% ispitanika je imalo inicijalnu bakterijsku infekciju donjih disajnih puteva, a prosečne vrednosti ispitivanih markera sistemske inflamacije su inicijalno na početku lečenja PTB bile signifikantno povišene u odnosu na kontrolnu grupu, da bi na kraju lečenja vrednosti brzine sedimentacije eritrocita u prvom satu (SE) i serumskog C-reaktivnog proteina (CRP) statistički značajno opale do subkliničkih vrednosti (SE- $p < 0,001$; CRP- $p < 0,001$), a vrednosti broja leukocita (Le) i serumskog fibrinogena signifikantno snizile i normalizovale (Le- $p < 0,001$; fibrinogen- $p < 0,001$). Multivarijantnom linearnom regresionom analizom dokazana je statistički značajna povezanost između vrednosti serumskog fibrinogena na početku lečenja PTB i pozitivne anamneze kontakta sa obolelim od TB i stepena radiološke proširenosti specifičnih plućnih promena na početku lečenja PTB.

Vrednosti markera akutno-faznog sistemskog inflamatornog odgovora imaju klinički značaj u proceni eventualanog nepovoljnog toka bolesti kod ekstenzivnih diseminovanih oblika PTB, kao i pojave komplikacija u smislu pridružene bakterijske superinfekcije.

Ključne reči: tuberkuloza, inflamacija, fibrinogen